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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,850	06/20/2007	Joan M. Robbins	022082-000610US	3709

20350 7590 12/23/2008

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,850	ROBBINS ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *258-265 and 267* is/are pending in the application.

4a) Of the above claim(s) *262 and 263* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *258-261, 264-265 and 267* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on September 9, 2008.

Status of Claims

Amendment of claim 258 and cancellation of claims 266 and 268-278 is acknowledged.

Claims 258-265 and 267 are currently pending and are the subject of this office action.

Claims 262-263 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 7, 2008.

Claims 258-261, 264-265 and 267 are presently under examination.

Priority

The present application is a 371 of PCT/US05/11046 filed on 04/01/2005, and claims priority to provisional applications No. 60/625,479 filed on 11/04/2004; No. 60/558,889 filed on 04/02/2004; and No. 60/658,745 filed on 03/04/2005.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated

(Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (Maintained Rejection)

Claims 258-261, 264-265 and 267 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hurwitz et. al. (Proceedings of the Annual Meeting of the American Society of Clinical Oncology, May 2003, cited by applicant, see title and abstract), Carlsson et. al. (The Cancer Journal (1997), 10:266-273, cited by applicant, and Anon (CAS accession No. 2003:518, corresponding to Clinical Breast Cancer (2003), 3:375-377).

The reasons for this rejection have been provided in the previous office action dated April 11, 2008, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant concedes that the substitution of 5,10-CH2FH4 (5,10-methylene tetrahydrofolate) for leuvocorin sets forth a proper *prima facie* case of obviousness. However, a legally proper prima facie case of obviousness can be traversed by evidence of surprising and advantageous results. Applicant then provides data that, according to applicant, demonstrates that the combination of the instant application:

5,10-CH2FH4, 5-FU and Avastin (bevacizumab) is superior to the one in the prior art: leucovorin (a precursor of 5,10-CH2FH4), 5-FU and Avastin (bevacizumab). In this regard, applicant points to some experimental results (example 2, Figures 7 and 8, and the results on pages 53-54) were the combination of the instant application and the one in the prior art are compared side by side. Applicant points to the data showing that the instant combination shows that the doubling time for tumor volume was reduced by more than one day, and that such differences could have not been predicted from the prior art, since the prior art describes 5,10-CH2FH4 and leucovorin as equivalents. Finally applicant points to some greater safety profile of the instant combination when compared to the prior art combination.

Examiner's response: the prior art clearly shows that the combination of 5,10-CH2FH4 with 5-FU is superior to the combination of leucovorin with 5-FU (see Carlsson, cited in prior office action, page 271, right column). Carlsson teaches that: median time of progression for patients being treated with 5,10-CH2FH4 with 5-FU against breast and gastrointestinal cancer was 8.8 months for all patients, which may be favorable in comparison to the approximately 5-6 months reported for leucovorin with 5-FU (see page 271, right column, middle of third paragraph). Carlsson further teaches that patients receiving 100 mg dose of 5,10-CH2FH4 with 5-FU have a significant longer median survival time compared with patients receiving the 200 mg dose (18.7 vs. 11.5 months) which is much higher than the median survival time of 11.5 months observed for patients treated with leucovorin with 5-FU (see page 271, right column, fourth paragraph). These results clearly show that the combination of 5,10-

CH2FH4 with 5-FU is superior when compared to leucovorin with 5-FU. As a consequence, it is expected that the combination of 5,10-CH2FH4 with 5-FU and Avastin (also known to treat breast cancer) should be superior to the combination of leucovorin with 5-FU with Avastin (already described in the prior art by Hurwitz et. al., cited in prior office action) for the treatment of breast cancer. In other words, the skilled in the art, knowing that a combination of 5,10-CH2FH4 with 5-FU can treat breast cancer more efficiently than a combination of leucovorin with 5-FU, and knowing that Avastin is also effective in treating breast cancer, will be motivated to treat breast cancer using two compositions (5,10-CH2FH4 with 5-FU and Avastin) known in the prior art to be useful for the same purpose (treat breast cancer), in order to form a third composition to be used for the very same purpose (*In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)), and the skilled in the art will expect that the 5,10-CH2FH4 with 5-FU and Avastin combination to be superior to the combination of leucovorin with 5-FU with Avastin for the reasons discussed above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
December 17, 2008

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612